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Review

# Sex differences in stroke: The contribution of coagulation

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ABSTRACT

Stroke is now the leading cause of adult disability in the United States. Women are disproportionately affected by stroke. Women increasingly outnumber men in the elderly population, the period of highest risk for stroke. However, there is also a growing recognition that fundamental sex differences are present that contribute to differential ischemic sensitivity. In addition, gonadal hormone exposure can impact coagulation and fibrinolysis, key factors in the initiation of thrombosis. In this review we will discuss sex differences in stroke, with a focus on platelets, vascular reactivity and coagulation.



**Contents**



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## Introduction

### *Stroke*

Each year, 15 million people worldwide are affected by stroke, resulting in 5 million deaths and 5 million cases of long-term disability. In the United States, stroke is the fourth most common cause of death and the leading cause of disability (Go et al., 2013). The American Heart Association predicts that by 2030, the direct cost of caring for stroke patients will triple from $61.55 billion to $183.13 million, due in large part to increasing life expectancy and expansion of the US aging population; after 55 years of age, the risk of stroke more than doubles for every subsequent decade of life (Ovbiagele et al., 2013). Evidence indicates that stroke is taking an increasingly heavy toll on the developed world due to increases in mortality, disability and the utilization of healthcare resources.

Ischemic stroke accounts for 87% of all stroke cases and is therefore an important target for novel preventive and therapeutic strategies (Go et al., 2013). Ischemic stroke is secondary to the formation of a thrombus, either in the symptomatic vessel or in the form of emboli from a more central source, such as the heart. Therefore, the balance between coagulation and fibrinolysis is a critical component of the disease. Thrombolysis is the only currently approved treatment for acute ischemic stroke and its effectiveness is greatly limited by common contraindications and a very narrow window of treatment. If a patient can be treated within 3 h of stroke onset and has no contraindications to treatment, the intravenous tissue plasminogen activator (tPA) should be administered in an attempt to enhance clot lysis and restore blood flow to the ischemic area (Wardlaw et al., 2003). Based on the results from ECASS III, a trial that examined the efficacy of an expanded treatment window, many centers in the US have extended their treatment window to 4.5 h, but as the drug is still only FDA approved for use within 3 h of stroke onset, consent must be obtained. Beyond this time, systemic tPA increases the risk of serious side effects, including intracerebral hemorrhage (Montano et al., 2013). Due to this narrow treatment window, less than 5% of acute stroke patients receive thrombolytic therapy (Zivin, 1999).

Angioplasty for clot disruption or mechanical removal of the clot is possible, but these therapies must be performed within 8 h of stroke onset and may only be available at advanced medical care centers (Nguyen-Huynh and Johnston, 2011). In addition, three recent randomized trials have called into question the efficacy of these therapies (Broderick et al., 2013; Ciccone et al., 2013; Kidwell et al., 2013). The limitations of currently available therapies and the projected increase in stroke prevalence highlight the urgent need for further research into targeted preventive strategies and novel acute therapies that can be used to treat patients outside the current therapeutic window.

### *Stroke: A sexually dimorphic disease*

Recent research demonstrates that women are disproportionately affected by stroke. It is the 3rd leading cause of death for women, compared to the 5th leading cause of death for men (Bushnell et al., 2014). In the United States, there are currently 26% more female stroke survivors than male and this disparity is expected to increase as the aging population continues to expand, with women increasingly outnumbering men in the elderly population (Go et al., 2013). This is due in part to the fact that women have a longer life expectancy, thereby increasing the incidence of stroke in the 55–75 female age group compared to their male counterparts (Seshadri et al., 2006).

Women have a lower incidence of ischemic stroke than men across most age groups, but in the highest age brackets (>85 years of age) women have higher stroke incidence (Petrea et al., 2009). In addition, women over 65 show a higher age-specific mortality rate from ischemic stroke than men (Ayala et al., 2002). Women are also more likely to be institutionalized following stroke and have poorer post-stroke outcomes (Gall et al., 2012; Paolucci et al., 2006). While social factors certainly play a significant role, men and women exhibit a wide variety of biological variances that may contribute to this intriguing disparity, including differences in genetics, hormonal factors and immune response.

### *Stroke pathophysiology*

Stroke is characterized by impaired delivery of oxygen and nutrients to brain tissues, resulting in devastating damage. The time from stroke onset to cellular death is dependent on the reduction in blood flow. The 'ischemic core' consists of tissue that receives cerebral blood flow of <10 mL/100 g per minute, resulting in rapid death of most cells within minutes, whereas blood flow between 10 and 20 mL/100 g per minute characterizes the 'ischemic penumbra'; these neurons are impaired, but still structurally intact and can regain function after blood flow has been restored (Baron, 2001). Oxygen and glucose deprivation in the ischemic core results in a rapid decline in production of neuronal ATP, which causes loss of the ionic gradient across the membrane and an increase in cytoplasmic $Na^+$ and $Ca^{2+}$ (Folbergrova et al., 1992). This increase elicits glutamate release, resulting in further $Ca^{2+}$ influx through NMDA and AMPA receptors until excitotoxicity occurs, resulting in cellular degeneration and necrosis (Haast et al., 2012). Although neuronal death does not occur in the penumbra, the high extracellular levels of glutamate from the ischemic core result in increased intracellular $Ca^{2+}$, increasing the activity of $Ca^{2+}$-dependent enzymes that produce apoptotic mediators like superoxide, arachidonic acid and nitric oxide (NO) (Sims and Muyderman, 2010).

Coagulation and thrombolysis are an integral part of both the pathology and treatment of ischemic stroke. Although there is significant evidence than men and women differ in coagulability and these differences are magnified during certain female-specific life events (such as pregnancy and menopause), there is a dearth of information regarding the potential contribution of coagulation differences to the sexual dimorphism of stroke incidence and outcome. In this review we will discuss sex differences in vascular reactivity, coagulation and therapeutic interventions as they relate to stroke.

## Sex differences in stroke: Separating chromosomal from hormonal

In order to fully elucidate the mechanisms behind the sexual dimorphism of stroke, it is important to recognize that males and females differ in both sex chromosome complement (XX vs. XY) and hormonal milieu. Although these factors are difficult to separate, it is important to recognize that sex differences in ischemic sensitivity may also be influenced by biologic sex (XX vs. XY) (Hagberg et al., 2004; McCullough et al., 2005; Renolleau et al., 2007; Yuan et al., 2009).

### *The dual role of sex hormones*

Estrogen and testosterone, the major sex hormones, have been shown to have both organizational and activational effects (Arnold,